

Catheter-associated recurrent intracardiac thrombosis and factor V Leiden mutation in a child with non-Hodgkin's lymphoma

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Patients with cancer have an increased risk for thromboembolism, which might be related to several factors including central venous catheters and chemotherapeutics. Congenital prothrombotic risk factors might also contribute to thrombotic events. In this report, we present a catheter-related recurrent intracardiac thrombosis in a boy with non-Hodgkin's lymphoma and factor V Leiden mutation. Screening for factor V Leiden mutation in children with cancer and recurrent thrombotic events is recommended. Periodic echocardiography may be considered for a group of patients if the catheter tip is in the right atrium and therapy includes L-asparaginase and corticosteroids.

Key words: recurrent intracardiac thrombosis, childhood cancer, factor V Leiden mutation.

Multiple risk factors contribute to the hypercoagulable state in cancer patients¹. Possible explanations for hypercoagulability in malignancy include increased procoagulant activity of tumor cells, comorbid conditions associated with cancer (such as immobilization, infection and stasis), surgery, use of central venous lines and effects of chemotherapy². On the other hand, when heterozygote individuals for congenital prothrombotic disease have thrombosis during childhood, there is usually a secondary challenge such as cancer or presence of central venous line^{3,4}. In this report, we present a catheter-associated recurrent intracardiac thrombotic event and factor V Leiden (FVL) heterozygote mutation in a child with non-Hodgkin's lymphoma (NHL).

Case Report

A 12-year-old boy was referred to our center for further treatment, having been diagnosed as NHL elsewhere. At initial presentation, he had cervical lymphadenopathies, subcutaneous nodules, left testicular enlargement and superior mediastinal syndrome. The diagnosis was confirmed and staging procedures were consistent with a stage III NHL. The immunophenotyping studies showed a T-cell phenotype.

The BFM-95 non-B cell chemotherapy protocol consisting of prednisolone, vincristine, adriamycin, L-asparaginase, cyclophosphamide, cytosine arabinoside and intrathecal methotrexate was started and he attained complete remission on day 33 of the first course of treatment. The routine echocardiograms as the part of the standard evaluation of anthracycline toxicity showed no abnormality.

A totally implanted subcutaneous device was inserted in the right subclavian vein on day 59 of the treatment and the catheter tip was seen in the right atrium on echocardiogram which was performed after the insertion. No abnormality was detected on repeated echocardiograms performed before each adriamycin dose. He received 12 doses of L-asparaginase treatment throughout all courses. The only complication related to the port was a partial obstruction at the 17th day of insertion, which resolved with local tissue plasminogen activator administration; thereafter, there was no occlusion or catheter-associated infection.

Four months after the port placement (on day 22 of protocol II), the right atrial mass was detected on a routine echocardiogram without any clinical symptoms. The mass, 21x23 mm

in diameter, was adhered to the right atrial wall with a thin pedicle (Fig. 1). Although the tricuspid valve was very close to the mass, there were no signs of right atrial outflow tract obstruction. The atrial mass had no relation with the catheter tip. The presumptive diagnosis was an atrial thrombosis. He had been in complete remission for 22 weeks and a lymphoma relapse at this site was very unlikely; however, a cardiac magnetic resonance imaging (MRI) was performed to obtain more details in order to rule out NHL relapse. MRI findings showed a large atrial mass which was consistent with an atrial thrombus.

To evaluate the hypercoagulable state of the patient, the following laboratory analyses were performed: anti-thrombin III, protein



Fig. 1. Echocardiogram showing right atrial mass.

C, protein S, factor VIII, antiphospholipid and antinuclear antibodies, homocysteine and lipoprotein a, activated protein C (APC), FVL and prothrombin gene mutations and lipid profile. We found he was heterozygous for factor V mutation [FVL mutation was analyzed by polymerase chain reaction (PCR) and allele specific oligonucleotide hybridization technique - Bio-Rad mD_x, USA] and he was found to have low APC ratio (0.6, normal range: 0.8-2.3) (APC resistance was analyzed by methods from Diagnostica Stago - France). On the other hand, he had high cholesterol (387 mg/dl, normal range: 109-189 mg/dl) and triglyceride (260 mg/dl, normal range: 36-138 mg/dl) levels, which became evident after corticosteroid therapy as part of a treatment protocol. The patient's past history and family history were uneventful for prothrombotic

disorders. Since he was heterozygous for FVL mutation, first-degree relatives were asked to consent to analysis for hypercoagulability state. His father and four-year-old brother were also shown to have heterozygous FVL mutation.

He was treated with low molecular weight heparin (LMWH) and underwent cardiomy. At the right atrium wall, two pink-white colored masses (2.5 and 1.5 cm in diameter) were detected which were closely located to the atrioventricular junction (Fig. 2). These masses were resected and the part adherent to the atrial wall was curetted. During the operation, the port was also removed and a thrombus at the catheter tip was seen. No complication developed during the operation or during the postoperative period. The pathological examination of the masses revealed organized thrombi which contained fibrin.



Fig. 2. On the right atrium wall, two masses which were closely located to the atrioventricular junction.

Afterwards, he was treated with heparin, and then oral anticoagulation was given with coumadin. During coumadin therapy, an INR level of 2.5-3.5 was maintained. There was no abnormality on follow-up echocardiograms. However, 22 days after the operation, while he was still on coumadin, a new thrombi (8 mm in diameter) was found in the left atrium which was closely located to the mitral valve. At the time of this second thrombotic event, he was receiving reinduction chemotherapy, and this treatment consisted of dexamethasone, vincristine and adriamycin. Initially, he was treated with heparin, and anticoagulant therapy was continued with coumadin. There was no change in the thrombus size, and no signs of cardiac dysfunction were evident on echocardiograms. He has been in continuous

complete remission for NHL for 22 months and has already been receiving maintenance therapy. The patient has been using coumadin for 15 months since the operation. We planned to continue oral anticoagulant therapy for a long period in view of the recurrent thrombosis.

Discussion

The association between cancer and venous thromboembolism is well established^{5,6}. The presence of central venous catheter is the single most important predisposing cause of thromboembolic disorder in children. Ruud et al.⁷ reported that 44% of the children with cancer and Hickman catheters developed neck vein thrombosis in their series, although the subcutaneous devices have been linked with a significantly lower rate of complication compared with percutaneous venous access⁸.

The occurrence of intracardiac thrombosis in a child with cancer and indwelling catheter is not a common event. However, a study searching for the prevalence of right atrial thrombi in children with cancer and indwelling catheters showed that 8.8% of these children had right atrial thrombi, and none of these children was symptomatic⁹. The incidence of right atrial thrombi is higher in cases with a catheter tip located in the right atrium in contrast to their positioning in the superior vena cava^{9,10}. Our patient had a subcutaneously implanted central venous access device with the catheter tip located in the right atrium.

The treatment protocol used for this patient included L-asparaginase and corticosteroids. The development of thromboembolic complications with L-asparaginase, which is an important antineoplastic agent for treatment of acute lymphoblastic leukemia (ALL) and NHL, is well documented, with the incidence ranging from 1.3 to 14.3%¹. The disproportionate reduction in natural anticoagulant levels, especially antithrombin, protein C and protein S, has been proposed as the pathogenic mechanism for the thromboembolic complications associated with L-asparaginase^{1,11}. In addition, corticosteroids that are commonly used in ALL and NHL treatment contribute to the risk of thrombosis by causing an increase in cholesterol and triglyceride levels, which is another risk factor for thromboembolism¹².

The presented case developed recurrent intracardiac thrombosis. Our search for additional risk factors revealed that he had

heterozygous FVL mutation. The FVL mutation has been identified as the most common inherited risk factor for venous thrombosis. A previous study found that the prevalence of FVL mutation in the healthy Turkish population is 10%¹³. The FVL mutation carrier state may often be asymptomatic, especially in children, and thrombosis usually develops when additional risk factors are present¹⁴. Sifontes et al.¹⁵ reported that the prevalence of FVL mutation in children with cancer was not different from that of the general population. This suggests that the mutation does not play a significant role in the overall pathogenesis of thrombosis in most children with cancer, but acquired APC resistance is common and may contribute to the thrombotic tendency in these patients^{2,15}.

Intracardiac thrombosis due to a mutation in the factor V gene has been rarely reported. Gürgey et al.¹⁴ reported on 63 children with thrombosis, and FVL mutation was found in 50% of the patients who had intracardiac thrombosis. On the other hand, cardiac disorders may lead to the development of intracardiac thrombosis. Gürgey et al.¹⁶ reported on 28 thrombotic children with cardiac disorders and showed that FVL and prothrombin gene mutations were found in 22% of these patients. Atalay et al.¹⁷ reported on 13 children with intracardiac thrombosis and found that patients with intracardiac thrombosis had an eight-fold higher risk carrying the FVL mutation than the normal healthy children. In the latter study, thrombi were localized in the right heart in nine patients and all children had a predisposing factor for thrombus formation such as ventriculo-atrial (V-A) shunts for hydrocephalus, indwelling catheter for chemotherapy or cardiomyopathy, sepsis, cardiac operation and homocystinuria. Although none of the five patients with cancer had FVL mutation, the authors recommended that screening for FVL mutation and other genetic risk factors should be included in all cases with intracardiac thrombosis¹⁷. In our patient, the multiple risk factors that may have contributed to the thrombotic process were having a malignant disorder, the presence of a subcutaneous port system with the catheter tip in the right atrium, receiving L-asparaginase and corticosteroids as part of the treatment protocol, and FVL mutation.

The therapeutic approach to a patient with thrombosis includes anticoagulation, thrombolysis, surgical thrombectomy and nonspecific supportive care^{4,18}. In the presented case, we did not use thrombolytic treatment, which is known to be effective at the early stage of thrombotic events. The size and the radiologic appearance of the thrombus were suggestive of an old and organized thrombus; therefore, it might have been resistant to thrombolytic treatment. On the other hand, the size of the thrombus was large and it was connected to the right atrial wall with a thin pedicle, so we thought thrombolytic therapy might cause fatal complications if this thin pedicle dissolved first. In the second thrombotic event, we aimed to avoid the possible complications of thrombotic treatment like bleeding during the early postoperative period of the patient. He was managed with LMWH during both thrombotic events. LMWH offers several advantages over standard anticoagulant therapy, including predictable pharmacokinetics, minimal monitoring and subcutaneous administration^{4,19}. After seven days of LMWH, he was given coumadin, which has been shown to be successful in preventing thrombosis in patients receiving chemotherapy²⁰. Since the patient had recurrent thrombosis, we considered long-term coumadin therapy as appropriate.

In conclusion, pediatric oncology patients may develop a thrombotic event at unusual sites like the right atrium. These children usually have both congenital and acquired risk factors for thrombosis. Although screening of children with cancer for FVL mutation is not routinely recommended, it should be investigated in cases of recurrent thrombotic events. Clinicians should also be aware of the risk for asymptomatic right atrial thrombi in cases with a catheter tip located in the right atrium. Periodic echocardiography may be considered for a group of patients, particularly if the catheter tip is in the right atrium and the therapy includes L-asparaginase and corticosteroids.

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